

D4

83, Ile 43, at positions Phe 17, Glu 64; at positions Phe 17, Ile 46, Ile 83, Glu 64; and at positions Ile 43, Ile 46, Ile 83, Glu 64.

### **REMARKS**

Claims 15 and 18-33 are pending.

#### **Claim Objections**

Claim 21 is amended to correct for informalities.

#### **Oath/Declaration**

In the prior Amendment and Response dated November 5, 2002, Applicant amended the specification to correct the claims of priority to the previously filed application from which this application was intended to take priority. Filed herewith is a request for correction of inventorship under CFR §1.48(a) and an unexecuted declaration and consent by assignee to change in inventorship. Applicant will subsequently submit an executed declaration and consent by assignee to perfect the claim of priority.

#### **Rejection under 35 U.S.C. §101**

Applicant respectfully contends that the claims are directed to statutory subject matter for reasons of record but have amended Claim 18 to include the term "non-naturally occurring" in the interest of expediting prosecution.

#### **Rejection under double patenting**

Applicant thanks the Examiner for permitting the postponement of the double patenting rejection until such time that the subject matter at issue is indicated as allowable.

#### **Rejection under 35 U.S.C. §132**

The Examiner has requested cancellation of the material added to the specification in the Amendment and Response dated November 5, 2002 under 35 U.S.C. §132. Applicant submits that the material added to the specification in the Amendment and Response dated November 5, 2002 is not new matter because it finds supports in the parent application, Serial No. 08/691,794, now U.S. Patent No. 6,057,418, herein incorporated by reference. Likewise,

the material added through the present amendment does not constitute new matter because it was present in the parent application, Serial No. 08/691,794, as filed.

Support for the added text can be found in U.S. Patent No. 6,057,428, for example, in column 4, line 25, through column 5, line 45. Additional support for the added text can be found in Example 2, column 41, line 37, through column 46, line 9.

**Rejection under 35 U.S.C. §112, first paragraph**

The Examiner rejected claims 19-33, directed to modification of amino acids Phe 17, Ile 46 and Ile 43, under 35 U.S.C. §112, first paragraph for lack of support in the specification. Applicant respectfully submits that claims 19-33 find support through reliance on the disclosure of the parent application, Serial No. 08/691,794. Additionally, the specification has been amended to provide express support for claims 19-33. Support for the added text can be found in U.S. Patent No. 6,057,428, for example, in column 4, line 25, through column 5, line 45. Additional support for the added text can be found in Example 2, column 41, line 37, through column 46, line 9.

The Examiner rejected Claims 18 and 15 under 35 U.S.C. 112, first paragraph for lack of enablement. Claim 18 has been amended to more clearly indicate that the modifications in the KDR and/or the FLT-1 binding regions result in a modification of the binding affinity of said region(s) with respect to binding affinity of KDR and or FLT-1 receptor(s) relative to the binding affinity of native VEGF. Applicant submits that the clarification addresses the Examiner's concerns and that amended claim 18, and dependent claim 15, are enabled by the specification.

**Rejection under 35 U.S.C. §102(b) and 35 USC §103**

Applicant respectfully contends that the rejections under 35 U.S.C. §102(b) and 35 U.S.C. §103 have been addressed by the addition of the term "non-naturally occurring" to Claim 18. As discussed above, amendment was made to Claim 18 in order to expedite prosecution.

**CONCLUSION**

Applicants respectfully submit that the claims are now in condition for allowance and early notification of such is earnestly solicited. If, upon review, the Examiner feels there are

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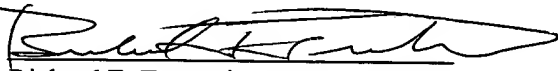
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additional outstanding issues which may be resolved by telephone, the Examiner is invited to call the undersigned attorney at (415) 781-1989.

Respectfully submitted,

DORSEY & WHITNEY, LLP

Dated: 2/18/03

By:   
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**VERSION SHOWING CHANGES MADE**

**IN THE SPECIFICATION:**

Please replace the first paragraph after the heading "Cross-Reference to Related Applications" at page 1, line 4, as amended by the transmittal accompanying the present application, with the following paragraph:

This is a continuation-in-part application of application Serial No. 08/567,200 filed December 5, 1995, now Patent No. 6,020,473 which issued February 1, 2000 and a continuation-in-part of application Serial No. 08/691,794 filed August 2, 1996, now Patent No. 6,057,428 which issued May 2, 2000, and claims the benefit of provisional application No. 60/002,827 filed August 25, 1995. The disclosures of Serial No. 08/567,200 and Serial No. 08/691,794 are expressly incorporated by reference.

At page 5, line 4, please insert the following paragraph, immediately after the paragraph entered in the Amendment and Response dated November 5, 2002:

In yet another embodiment of the invention, mutagenesis is effected at one or more of the positions Ile 46, Gln 79 and Ile 83 and/or Ile 43, Phe 17 and Glu 64 of a nucleic acid encoding a vascular endothelial cell growth factor (VEGF) variant of native VEGF. By way of example, the following nucleic acids encoding VEGF variants are further embodiments of the invention: nucleic acids encoding VEGF variants having modifications at positions Ile 46, Gln 7, Ile 83, Ile 43, Phe 17 and Glu 64; at positions Ile 46, Ile 83, Glu 64; at positions Phe 17, Gln 79, Ile 43; at positions Ile 46, Gln 79, Ile 83, Ile 43, Phe 17 and Glu 64; at positions Ile 46, Gln 79, Ile 83, Ile 43, at positions Phe 17, Glu 64; at positions Phe 17, Ile 46, Ile 83, Glu 64; and at positions Ile 43, Ile 46, Ile 83, Glu 64.

**IN THE CLAIMS:**

15. (Twice Amended) The composition of matter of Claim 18, wherein said carrier is a pharmaceutically acceptable carrier.

18. (Twice Amended) A composition of matter comprising a purified polypeptide, said polypeptide comprising:

a) a purified polypeptide, said polypeptide comprising a non-naturally occurring vascular endothelial cell growth factor (VEGF) variant of native VEGF wherein said variant differs from native VEGF in that said variant contains at least one modification in the Kinase domain region (KDR) and/or FMS-like Tyrosine Kinase region (FLT-1) ~~such that the binding affinity of said region(s) is modified with respect to binding affinity of KDR and or FLT-1 receptor(s) with native VEGF~~, said modification(s) resulting in a modification of the binding affinity of said region(s) with respect to binding affinity of KDR and or FLT-1 receptor(s) relative to the binding affinity of native VEGF; and

b) a carrier.

19. (reiterated) A nucleic acid encoding a polypeptide, said polypeptide comprising a vascular endothelial cell growth factor (VEGF) variant of native VEGF, wherein said native VEGF comprises amino acids Ile 46, Gln 79 and Ile 83 and/or Ile 43, Phe 17 and Glu 64 and said variant differs from said native VEGF by having at least one of said amino acids modified to form said variant, said polypeptide exhibiting functionally reduced binding affinity to KDR as compared to the binding affinity of native VEGF to KDR.

20. (reiterated) The nucleic acid according to Claim 19 wherein each of said amino acids is modified.

21. (Twice Amended) The nucleic acid according to Claim 19 wherein two or more of said amino acids ~~is~~ are modified.

22. (reiterated) The nucleic acid according to any one of Claims 19, 20, or 21 wherein the amino acid modification is a substitution by alanine.

23. (reiterated) The nucleic acid according to Claim 19 wherein Ile 46, Ile 83, Glu 64 of said native are modified.

24. (reiterated) The nucleic acid according to Claim 23 wherein said amino acid modification is a substitution by alanine.

25. (reiterated) The nucleic acid according to Claim 19 wherein Phe 17, Gln 79, Ile 43 of said native are modified.

26. (reiterated) The nucleic acid according to Claim 25 wherein said amino acid modification is a substitution by alanine.

27. (reiterated) The nucleic acid according to Claim 19 wherein Ile 46, Gln 79, Ile 83, Ile 43 of said native are modified.

28. (reiterated) The nucleic acid according to Claim 27 wherein said amino acid modification is a substitution by alanine.

29. (reiterated) The nucleic acid according to Claim 19 wherein Phe 17 and Glu 64 of said native are modified.

30. (reiterated) The nucleic acid according to Claim 19 wherein Ile 46, Gln 79, Ile 83, Ile 43, Phe 17, Glu 64 of said native are modified.

31. (reiterated) The nucleic acid according to Claim 19 wherein Phe 17, Ile 46, Ile 83, Glu 64 are modified.

32. (reiterated) The nucleic acid according to Claim 19 wherein Ile 43, Ile 46, Ile 83, Glu 64 of said native are modified.

33. (reiterated) The nucleic acid according to Claim 29, 30, 31 or 32 wherein said amino acid modification is a substitution by alanine.